Polycystic ovarian syndrome (PCOS) in the Adolescent Girl

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Summary: **PCOS is an endocrinopathy. It is associated with increased androgen secretion, hirsutism, menstrual irregularities and infertility. It has its origin in adolescence. Amongst its various signs and symptoms obesity is the only one towards which preventive steps can be taken. Insulin has a role on the pathophysiology of PCO. Insulin resistance is a matter of ongoing research and further studies are needed to determine its exact role. PCOS is significant not only its symptoms but also because it has an impact on the future health of the adolescent girl.**

Introduction

Polycystic ovarian disease is the commonest endocrine disorder in women of reproductive age. It is diagnosed in 5-10% of women between adolescence and menopause. This condition frequently has its origin in adolescence. It is associated with increased androgen secretion, hirsutism, menstrual irregularities and infertility. It has an impact not only on the physical but also on the mental health of the young girl. Female adolescence is normally accompanied by the increased adrenal and ovarian production of androgens. It is not uncommon in early to mid puberty to see typical feature of PCOS. At present no single prospective test can differentiate girls in whom this maturational process is self limiting from those in whom it will progress to adult PCOS with all its consequences.

Clinical presentation.

Polycystic ovary syndrome is characterized clinically by a history of chronic anovulatory bleeding in combination with some evidence of androgen excess, such as hirsutism, acne, elevated serum androgen concentrations, or a combination of these. This clinical definition is based on the Consensus Conference of the National Institute of Health and National Institute of Child Health and Development held in 1990(Zawedzki and Dunaif 1992) The consensus was that there are "definite or probable" criteria for the diagnosis of polycystic ovary syndrome. Definite criteria included menstrual dysfunction and androgen excess and excluded congenital adrenal hyperplasia and other causes. Factors such as insulin resistance, elevated ratio of luteinizing hormone (LH) to follicle stimulating hormone (FSH) and ovaries appearing polycystic on ultrasonography were connsidered to be "probable criteria."

Goldheizer and Green (1963) observed that in clinical practice, women with polycystic ovary syndrome are seen for three major reasons: Infertility (mean incidence 74%) menstrual irregularity (mean incidence of dysfunctional bleeding 29%, mean incidence of amenorrhea 51%), and androgen excess (mean incidence of hirsutism 69% mean incidence of virilisation, 21%)

In our personal experience of adolescent girls over 1996 1998 i.e. three years, the prevalence of polycystic ovaries on ultrasound was approximately 30%. Amongst the girl having polycystic ovaries, on ultrasound, 50% had evidence of hyperandrogenism [hirsutism and / or acne], 25% were overweight, and 91% had menstrual irregularity [regular or delayed periods and secondary amenorrhoea].

Pathophysiology

The fundamental pathophysiologic defect in polycystic ovary syndrome remains unknown and is a source of controversy and ongoing study. However, the key features include insulin resistance, androgen excess, and abnormal gonadotropin levels. There is a linear correlation between serum androgen levels and measures of hyperinsulinemia (Burghen et al 1980).

PCOS clusters within the families and if a girl in such a family has PCOS then the risk of the syndrome in her sister is about 50% compared to a population prevalence of only 10% for such a risk (Davison 1998). The mode of inheritance is uncertain and no gene variants have been clearly demonstrated to contribute to the inherited susceptibility.

Diagnosis

The diagnosis of poycystic ovary syndrome depends on confirming the presence of hyperandrogenism and excluding other causes of hyperandrogenic anovulation. A careful history is the first step in making a diagnosis. The pattern of hair distribution should be documented. The neck, axilla, and groin should be inspected for acanthosis nigricans, a classic manifestation of insulin resistance. Recently, Koskinen et al (1996) demonstrated that elevated ratio of luteinizing hormone to follicle stimulating hormone in combination with an elevated androstenedione level yielded the greatest diagnostic sensitivity and specificity. It is important to consider other causes of hyperandrogenism, such as ovarian or adernal tumors, congenital adrenal hyperplasia and Cushing syndrome. Also, hyperprolactinemia, hyperthyroidism and hypothyroidism must be excluded.

Once the diagnosis is made, the physician must look for serious concomitant lipoprotein derangements, insulin resistance and hyperglycemia. Adams et al (1986) established sonographic criteria-multiple small subcapsular follicles and increased central stroma. Although as many as 20% of healthy women have polycystic morphologic features on ultrasonography, only fraction of these women have the endocrine abnormalities of hyperandrogenemia and menstrual irregularities (Polson et al 1998, and Farquhar et al 1994). Rajaniemi et al (1980) consider an LH/FSH ratio in the range 3:1 to be diagnostic of polycystic ovary syndrome. Fox et al (1992) and Robinson et al (1992) also have shown that the best indicator of PCOS (Ovarian morphology consistent with polycystic ovaries combined with oligomenorrhea) is circulating androgen value rather than gonadotropin measurement. Robinson et al (1992) have also shown that total testosterone level has a sensitivity of 70% and the free androgen index has sensitivity of 94%.

Health Issues

Role of Insulin

Insulin has a modulating action on various parts of the reproductive endocrine system by acting like a non-pituitary gonadotroph along with several paracrine growth factors. PCOS is associated with hyperinsulinism secondary to insulin resistance. As a consequence these patients have cardio-vascular risk factors, impaired glucose tolerance, diabetes, hyperlipidemia, hypertension and abdominal obesity. Over 30% of lean and 75% of obese women with PCOS are hyperinsulinaemic (Davison 1998). 40% of women with PCOS devlop impaired glucose tolerance or frank diabetes by the age of 40.

Cardiovascular risk

Talbot et al (1995) observed that the cardiovascular risk factors in women with PCOS are: increased body mass index, increased insulin, decreased HDL_1 and HDL_2 Cholesterol with increased LDL and increased waist/hip ratio and increased triglycerides.

Obesity

Obesity is an important diagnostic criterion and represents the capacity to convert androgens to estrogen in peripheral fat issue. Weight is expressed as BMI (Body mass index). Overweight is defined as BMI>25. It has been noted that more then 80% of the patients found to have PCOS were obese prior to puberty. Obesity occurs in only 35-60% of girls with PCOS and clearly all obese girls do not have hormonal disturbance.

Balen et al (1995) were able to show that in 1741 women with PCOS all those who had PCO on sonography, 38.4% had BMI associated with a rise in serum testosterone concentration, increased incidence of amenorrhoea, infertility and hirsutism. Obesity also directly leads to various problems like hernia, osteorthrosis, varicosity

etc., in adult life. Hence reduction of weight should be encouraged in all obese young girls.

Endometrial hyperplasia and cancer

PCO is associated with chronic anovulation. Hence there is unopposed estrogen action on the uterus as there is no progesterone produced.

Therefore these women are at a higher risk of endometrial hyperplasia and cancer. Hence young girls who have PCOS and delayed periods should be administered progesterone therapy at regular intervals to reduce menstrual loss and also to prevent endometrial hyperplasia in future.

Bone disease

Young girls with PCO have adequate estrogen levels inspite of their anovulation therefore risk of osteoporosis is low in adult life.

Treatment

The therapeutic approach to polycystic ovary syndrome depends on patient symptoms, etiologic considerations, motivation and objectives. Treatment decisions hinge on whether the patient is seeking immediate fertility. If fertility is not an immediate goal, as in adolescent girls, then treatment goals fall into two broad categories. The first is symptom management of hirsutism, acne and oligomenorrhea. The second is assessment and amelioration of health risk. Weight loss is the most natural method for increasing insulin sensitivity.

Another approach to manipulating insulin action is to employ an insulin-sensitizing agent. The initial experience with these agents has been controversial. There are no large-scale randomised placebo controlled trials to support their recommendation as frontline treatment of patients with PCOS. Numerous studies have been conducted with metformin. It is a biguanide that lowers blood glucose levels so its effects on insulin action is secondary. It works primarily by suppressing hepatic gluconeogenesis. The most carefully conducted trial was that by Ehrrmann et al (1997), who found that hyperinsulinaemia and androgen access were not improved when metformin was taken for three month Nestler and Kakubawieg (1996) have reported that it decreases insulin levels and thus hyperandrogenemia. Studies in patients with PCO treated with metformin have shown resumption of menses and weight loss. It is difficult in these cases to separate the effects of weight loss on insulin action from those of the medication. Velazquez et al, (1997) examined menstrual regularity in patients with polycystic ovary syndrome who were treared with Metformin. Twenty-two patients received 1500mg of metformin for a period of 6 months. They reported a statistically significant difference in the free testosterone levels and resumption of regular menses Pregnancies have also been reported with the use of metformin though the numbers are small.

Troglitazone is a thiazolidinedione group of insulin sensitizing agent. Ehrmann et al (1997) showed that it might be beneficial in mangement of PCOS. Both drugs have side effects that require careful monitoring Metformin has been associated with nausea, abdominal discomfort, diarrhea, and anorexia. Troglitazone has been associated with elevated liver function test result (<2% of patients) and in extremely rare cases, hepatic necrosis.Troglitazone had to be withdrawn from the market due to death from hepatic dysfunction.

Another possible problem with these drugs is the possibility of teratogenic effects. Lean women with PCOS who are not absolutely insulin resistant or hyperinsulinemic may not tolerate all antidiabetic agents, and they may therefore require special consideration.

The ideal agent for the treatment of PCOS would reduce androgen secretion, improve metabolism and dyslipidemias, and produce regular ovulatory cycles. When planning treatment regimens for women with PCOS, the obstetrician-gynecologist must consider patient preference and motivation regarding cosmesis and conception versus contraception, cardiovascular disease risk factors, and the degree of glucose intolerance. Because no "magic bullet" exists, as combination of therapies may be warranted at any given time or across time as patient conditions or objectives change.

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